Faculty of Health Sciences — Department of Medicine | Queen's University

Queen's UNIVERSITY

GIDRU Report 2019/20

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MESSAGE FROM THE DIRECTOR

Photo Credit: Matthew Manor

With our CFI/OIT-funded 'human' research laboratory now fully operational—including our state-of-the-art 'chemostat facility', 'metabolomics centre' and 'biobanking facility'—we are conducting translational (bench-to-bedside) and reverse-translational studies (bedside-to-bench), leading to exciting discoveries that are advancing the well-being of Canadians and of patients worldwide.

This report captures GIDRU's ongoing research excellence that has been building for almost 60 years and has allowed our group to be recognized internationally as one of the few sites in the world conducting research that fully integrates preclinical and clinical gastrointestinal studies. With our CFI/OIT-funded 'human' research laboratory now fully operational—including our state-of-the-art 'chemostat facility', 'metabolomics centre' and 'biobanking facility'—we are conducting translational (bench-to-bedside) and reverse-translational studies (bedside-to-bench), leading to exciting discoveries that are advancing the well-being of Canadians and of patients worldwide. This work has been enabled by our investigators' ability to successfully compete for Tri-Council funding and other major external, peer-reviewed grants. We have established strong collaborations with our colleagues at Queen's through the TIME network, as well as with researchers nationally and internationally, thereby sharing our expertise and likewise benefiting from the complementary expertise of others. We continue to build for the future by attracting talented new faculty and by recruiting exceptional students from around the world, who, following their training, are securing leading positions in science and medicine.

Dr. Stephen Vanner
Director of GIDRU

EXECUTIVE SUMMARY

GIDRU Executive Summary

- Core basic and clinician-scientist members continued to attract almost $1M annually in peer-reviewed funding, publishing > 50 papers in 2019/2020, with 30% of the journals having an impact factor > 5
- Ongoing international recognition for basic and translational innovations and discoveries, including first-in-the-world experiments using "synthetic" stool transplant microbiome therapy to cure *Clostridioides difficile* colitis and the most highly cited paper in our subspecialty studying diet-microbiome interactions in irritable bowel syndrome (IBS) patients
- Co-leads of a $25M Canadian Institutes of Health Research-Strategy for Patient-Oriented Research (CIHR-SPOR) initiative examining IBS and inflammatory bowel disease (IBD) patients, with $1.8M directed to Queen's
- Good Clinical Practice (GCP) – accredited clinical trial unit conducts over 10 high-quality trials annually totaling over $500k, comprised of both investigator- and industry – initiated trials
- Awarded $3M by Canada Foundation of Innovation/ Ontario Innovation Trust (CFI/OIT) to expand its translational research by building the "Human Laboratory for the Study and Treatment of Gastrointestinal Disorders" that is now fully operational and includes a cutting-edge chemostat facility, newly established metabolomics centre for clinical research, and a high-capacity biobanking facility with over 500 enrolled patients
- Received $2.2M (cash and in-kind support) from Industrial Partners to open a state-of-the-art research endoscopy suite at Kingston Health Sciences Centre (KHSC) – Hotel Dieu Hospital (HDH) site
- With generous support from B'Nai Brith, established an endoscopy-training centre that was the first in Ontario and second in the country to develop competency-based training programs and undertake peer-reviewed educational research
- Trained > 30 MSc, PhD, undergraduate students and basic science and clinical PDFs in 2019/2020
- Expanded GIDRU's capacity and translational potential through membership in the new Queen's Translational Institute of Medicine (TIME) department, superuser membership in QCPU, developing three new multidisciplinary partnerships within the Faculty of Health Sciences, and continued expansion of GIDRU's associate membership
- Recruited two new GI clinician-scientists to sustain the GIDRU core clinician-scientist faculty
- Made significant contributions to Crohn's and Colitis Canada and the Canadian Digestive Health Foundation national fundraising programs
- Promoted public awareness and education of GI disorders through local, national, and international presentations via public meetings, televised programing, and live internationally-subscribed webinar platforms

Brief History of GIDRU

SECTION I

60 Years in the Making

1960s

GIDRU's roots lie in the Division of Gastroenterology and can be traced back to the arrival of Dr. Ivan Beck at HDH, who was joined by Drs. Larry DaCosta and Peter Dinda, a basic scientist and life-long collaborator of Ivan's. In parallel, Dr. Leslie Valberg established a program at the Kingston General Hospital (KGH) and was subsequently joined by Drs. Simon, Groll, and later, Depew.

1982

GIDRU was formally launched as a multidisciplinary research group under Dr. Ivan Beck's leadership with members from the GI Division, Biology, General Surgery, and Immunology. The facility received generous support from HDH and the Jeanne Mance Foundation.

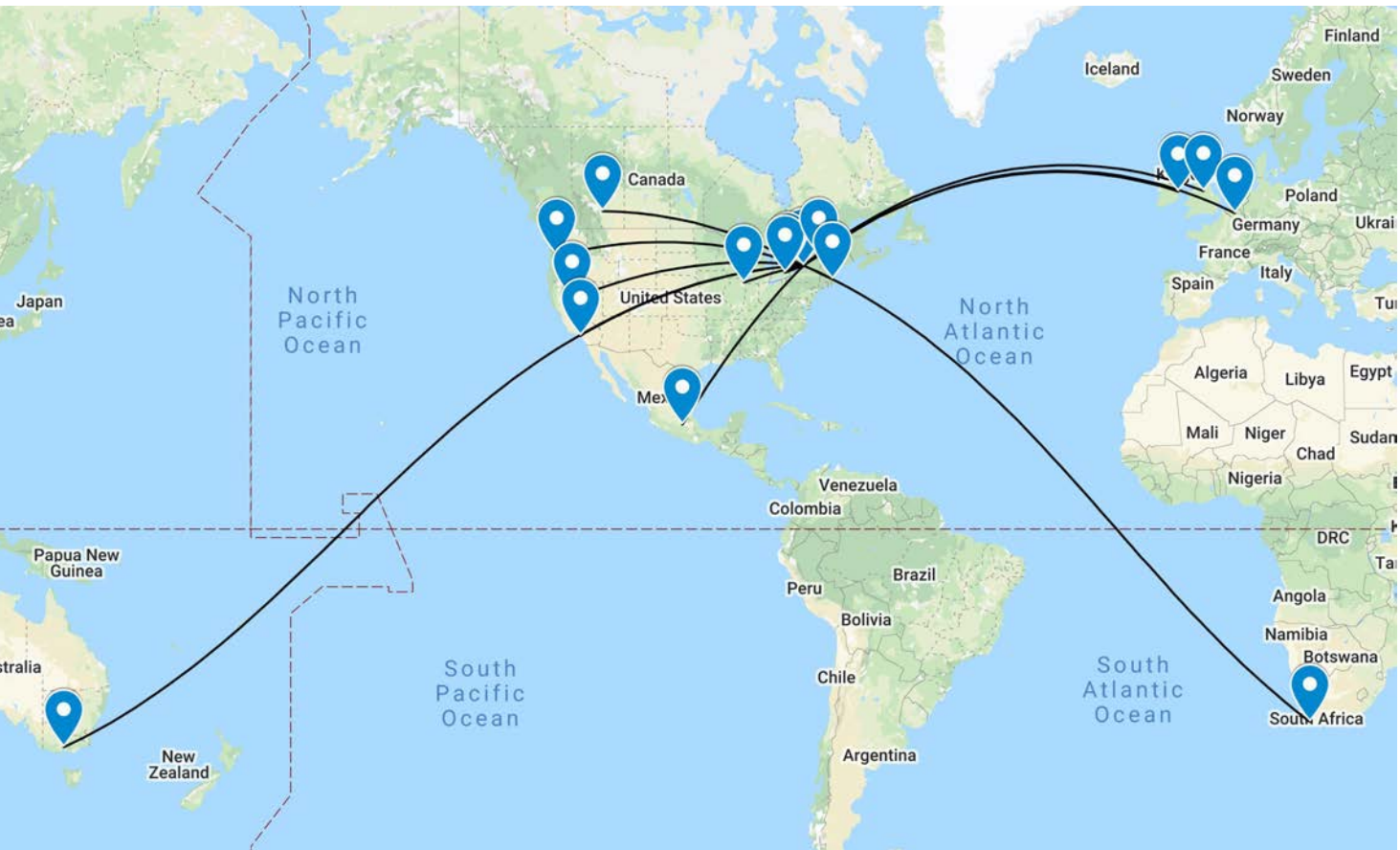
GIDRU in 1987

1990 – 2000

Under Dr. William Paterson's leadership, GIDRU enjoyed pivotal successes that elevated GIDRU's stature internationally. For instance, GIDRU was awarded funding in a national competition to establish the first GI motility education centre in Canada; received the first CIHR training award in Canada to establish a centre for training in Digestive Sciences, followed by a CFI/OIT award to build and equip a new 8000 sq ft cutting-edge research facility. With the support of the KGH and Queen's University, the GIDRU facility was constructed at the KHSC – KGH site in 2007.

2001 – present

Dr. Stephen Vanner oversaw a period of significant expansion of the GIDRU faculty. Recruitment efforts attracted experts worldwide, as well as from within the Queen's faculty. The recruitment of the best and brightest continues with the recent addition of Dr. Prameet Sheth PhD, a medical microbiologist and clinician-scientist who now leads the microbiome and chemostat research program at GIDRU. Also, Dr. Dan Mulder MD PhD, who is a pediatric gastroenterologist finishing his clinician-scientist training, will open his inflammatory bowel disease laboratory in GIDRU in 2021. Another recent recruit, Dr. Robert Bechara trained in Japan to develop a leading North American program to perform peroral endoscopic myotomys (POEMs) and has now joined Dr. Hookey in conducting endoscopic research.
GIDRU's translational capacity has also been significantly increased through the fully operational "Human Laboratory for the Study and Treatment of Gastrointestinal Disorders" funded by CFI/OIT. It includes a research endoscopy suite with biobanking facilities for human samples, a state-of-the-art chemostat facility led by Dr. Sheth, a new metabolomics centre in the W.J. Henderson Patient-Oriented Research Centre located at the KHSC – KGH site, and a high-capacity biobanking facility at the KHSC – HDH site, with over 500 urine, blood, and stool samples already enrolled from highly phenotyped patients. GIDRU's leading-edge infrastructure and expertise led to its investigators being chosen as co-leads on a $25M CIHR-SPOR initiative called IMAGINE (Inflammation, Microbiome, and Alimentation: Gastro-Intestinal and Neuropsychiatric Effects), with $1.8M directly supporting GIDRU.



DIVISION OF GASTROENTEROLOGY

GIDRU's roots are deeply embedded in the Division of Gastroenterology and the division continues to provide the leadership and nucleus for the research unit. The members of the division specialize in clinical disciplines: Hookey, Bechara (Therapeutic endoscopy); Reed, Beyak, Vanner (GI motility); Beyak, Ropeleski (IBD); Sheth (Microbiome); Louw (Dyspepsia and *Helicobacter pylori* infection); Flemming, Lowe, Kelly (Hepatology). All members participate in GIDRU through clinician-scientist roles, PI-directed research programs, clinical trials, or collaborative roles.

Robert Bechara
Assistant Professor

Michael Beyak
Assistant Professor

Michael Blennerhassett
Professor

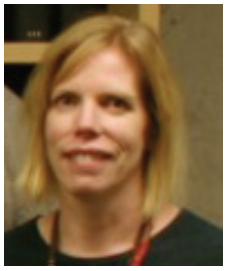
Jennifer Flemming
Assistant Professor

Lawrence Hookey
Professor
Division Chair

Melissa Kelley
Assistant Professor
Director, Clinical Trials

Alan Lomax
Professor

Jacob Louw
Professor



Catherine Lowe
Assistant Professor

David Reed
Assistant Professor

Mark Ropeleski
Associate Professor
Program Director

Prameet Sheth
Assistant Professor

Dr. Stephen Vanner
Director, GIDRU and TIME

Funding

SECTION II

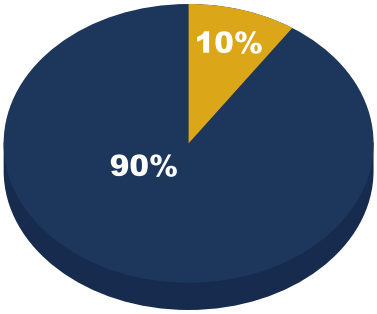
GIDRU has maintained its levels of peer-reviewed and industry-derived support. Furthermore, GIDRU researchers have won a substantial CFI / OIT award to develop facilities for greatly expanded patient-oriented research, including dedicated research endoscopy, microbial therapeutic research and human tissue biobanking

FUNDING DETAILS

The GIDRU core members received over $6M in research funding in the period 2012-2013. These funds were obtained through competitive peer-reviewed funding sources, investigator- and industry-driven clinical trials and technology transfer to Industry. The following figures highlight the relative proportions and sources of peer-reviewed funding.

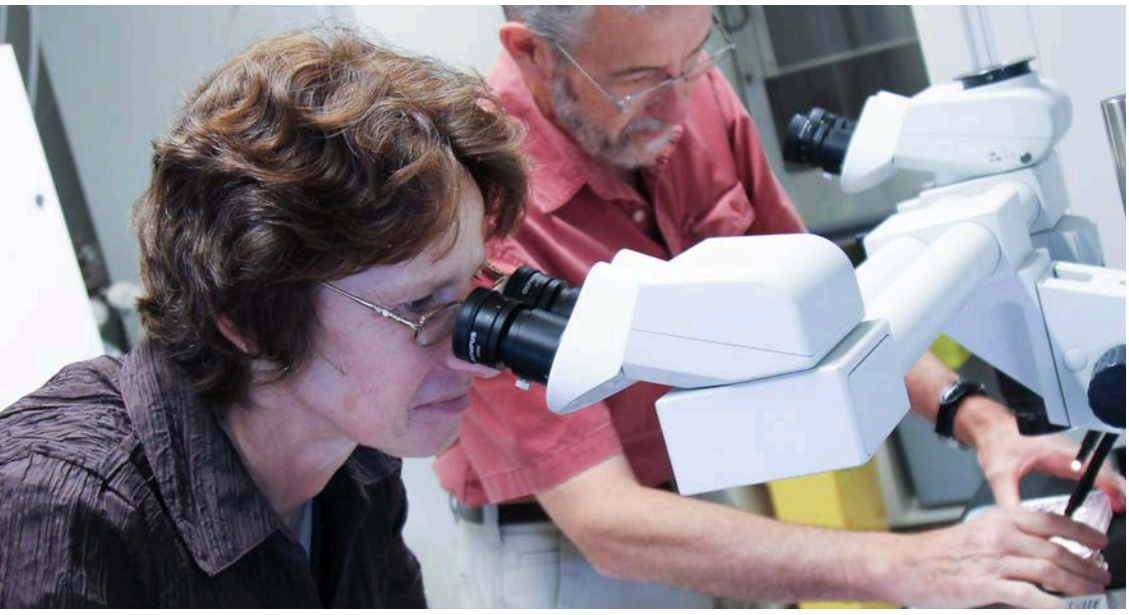
17% Internal ($324k)
83% External ($1.6M)

GIDRU Funding (2019 - 2020)



10% Internal ($655k)
90% External ($5.8M)

GIDRU Funding (~ Past 5 yrs)



FUNDING DETAILS

Bechara

Current Funding

2020/05 – 2022/04
Principal Investigator – Innovation Fund, Operating Grant - $173,694 (CAD)
Fistulotomy as the primary cannulation technique for all patients undergoing ERCP: A randomized controlled trial
Southeastern Ontario Academic Medical Organization (SEAMO)

2017/03 – 2020/06
Principal Investigator – Operating Grant - $24, 736 (CAD)
The use of POEM to characterize clinical-pathological correlation in achalasia
Division of Medicine Research Award Grant

Blennerhassett

Current Funding

2016 – 2021
Principal Investigator – Operating Grant - $34,000 p.a. (CAD)
Neuro-muscular innervation in neonatal intestinal development
Natural Sciences and Engineering Research Council of Canada (NSERC)

Flemming

Current Funding

2020/04-2022/03
Co-Investigator – Innovation Fund - $132,900 (CAD)
Screening patterns and the identification of non-alcoholic fatty liver disease in obese children in Canadian primary care
SEAMO
Principal Investigator: Kehar, Mohit

2019/08-2022/07
Principal Investigator – Operating Grant - $25,000 (CAD)
Characterizing fatty liver disease in adolescents and young adults: A prospective feasibility study
TIME, Queen's University

2019/06-2021/05
Co-Investigator – Operating Grant - $18,849 (CAD)
Epidemiology of pediatric cirrhosis in Ontario: A population-based study
Clinical Teachers Association of Queen's University
Principal Investigator: Kehar, Mohit

2018/07-2020/06
Principal Investigator – Clinical, Translational, and Outcomes Research Award - $268,503 (CAD)
Epidemiology, natural history and healthcare utilization in young adults with cirrhosis (ENHAnCe): A population-based study
American Association for the Study of Liver Disease (AASLD)

2018/6-2021/5
Principal Investigator – Operating Grant - $24,137 (CAD)
Defining the etiology of cirrhosis in young adults in Ontario
Department of Medicine Innovation Fund – Queen's University

Funding applied for

Co-Investigator – Project Grant Spring 2020 - $595,000 (CAD)
Explaining regional variation in colon cancer survival through factors in the continuum of cancer care
Canadian Institutes of Health Research (CIHR)
Principal Investigator: Groome, Patti

Co-Principal Investigator – Operating Grant - $30,000 (CAD)
ACCESS-LT
Canadian Donation and Transplantation Program
Co-Principal Investigator: Selzner, Nazia

Principal Investigator – Operating Grant - $23,690 (CAD)
Pregnancy in women with hepatitis C: A Population-based cohort study
Department of Medicine - Queen's University

Principal Investigator – Operating Grant - $66,690 (CAD)
Derivation and validation of a risk prediction tool for mortality after non-hepatic abdominal surgery in patients with cirrhosis
Canadian Liver Foundation

Co-Principal Investigator – Operating Grant - $58,749 (CAD)
Trends in the incidence and management of hepatocellular carcinoma in Ontario: Do treatment and survival according to region justify centralized treatment?
Canadian Liver Foundation
Principal Investigator: Sapisochin, Gonzalo

Hookey

Current Funding

2019/02 – 2019/06
Principal Investigator – Innovation Fund – $16,800 (CAD)
"Is Needle Knife Fistulotomy An Effective First Step Strategy for All ERCPs?"
Academic Health Science Centre Alternative Funding Plan (AHSC AFP) Innovation Fund

2019/02 – 2019/06
Principal Investigator – Innovation Fund – $16,800 (CAD)
"Is Needle Knife Fistulotomy An Effective First Step Strategy for All ERCPs?"
AHSC AFP Innovation Fund

Lomax

Current Funding

2019-2024
Principal Investigator – Project Grant - $180,000 p.a. (CAD)
Modulation of pain in IBD by microbial proteases
CIHR

2019-2022
Co-Principal Investigator – Grants in Aid of Research - $125,000 p.a. (CAD)
Reducing IBD pain: targeting novel opioid G protein-coupled receptor signaling in DRG neurons
Crohn's Colitis Canada (CCC)
Principal Investigator: Vanner, Stephen

Funding applied for

2020-2022
Co-Principal Investigator – Weston Family Microbiome Initiative - $100,000 p.a. (CAD)
A Jekyll and Hyde Role for microbial proteases in the regulation of pain
The W. Garfield Weston Foundation
Co-Principal Applicant: Reed, David

2020-2025
Co-Applicant - Project Grant - $200,000 p.a. (CAD)
Beyond the microbiota: Neuroactive mediators underlying chron-ic abdominal pain
CIHR
Principal Investigator: Vanner, Stephen

2020-2023
Co-Applicant – Grant in Aid of Research - $125,000 p.a. (CAD)
Role of cannabinoid receptors to treat pain in IBD
CCC
Principal Investigator: Reed, David

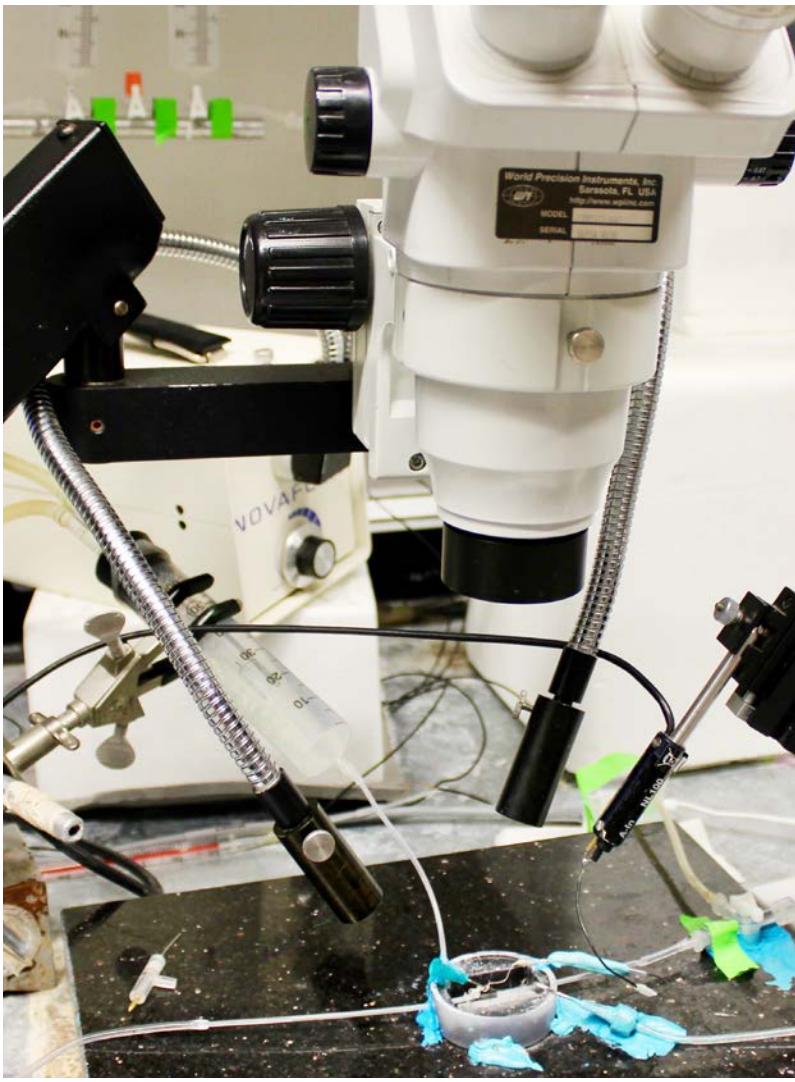
2020-2022
Co-Applicant – Weston Family Microbiome Initiative - $200,000 (CAD)
Identification and characterization of novel therapeutic protease(s) for the treatment of *Clostridioides difficile* infection
The W. Garfield Weston Foundation
Principal Investigator: Sheth, Prameet

Reed

Current Funding

2020/05 – 2021/04
Co-Investigator – Innovation Fund - $36,000 (CAD)
The application of metabolomics to enhance detection of COVID-19 and predict disease severity: A proof-of-principle study
SEAMO
Principle Investigator: Vanner, Stephen

2020/03 – 2021/02
Principal Investigator – Ironwood IBS Innovation Award - $30,000 (USD)
Using metabolomic profiles to study mechanisms of nociceptive signaling in subsets of IBS diarrhea predominant patients
American Neurogastroenterology and Motility Society (ANMS)



2019/08 – 2022/07
Principal Investigator – TIME Incubator Grant - $75,000 (CAD)
Psychological stress-food antigen triggers IBS symptoms via loss of oral tolerance
TIME

2019/07 – 2022/06
Co-Investigator – Grant in Aid of Research - $375,000 (CAD)
Reducing IBD pain: targeting novel opioid G protein-coupled receptor signaling in DRG neurons
CCC
Principal Investigator: Vanner, Stephen

2019/07-2021/06
Principal Investigator – Endowment Fund (Operating Grant) - $20,000 (CAD)
Mechanism of mast cell activation following stress-food antigen in IBS model
Clinical Teachers Association of Queen's University (CTAQ)

2019/07-2021/06
Principal Investigator – Innovation Fund - $78,000 (CAD)
Metabolomics: Moving beyond symptoms to phenotype irritable bowel syndrome
SEAMO

2019/04 – 2024/03
Co-Investigator – Project Grant - $180,000 p.a. (CAD)
Modulation of pain in IBD by microbial proteases
CIHR
Principal Investigator: Lomax, Alan

2018/01 – 2021/01
Principal Investigator – Innovation Fund - $30,000 (CAD)
Diet-microbiome interaction modulates colonic nociceptive signaling in IBS
Queen's University Department of Medicine

2017/05 – 2022/04
Co-Investigator – Project Grant - $688,500 (CAD)
Novel signaling mechanisms leading to pain in irritable bowel syndrome
CIHR
Principal Investigator: Vanner, Stephen

Funding applied for

2020/07 – 2023/06
Principal Applicant – Grant in Aid of Research - $375,000 (CAD)
Role of cannabinoid receptors to treat visceral pain in IBD (Under Review)
CCC

Sheth

Current Funding

2020 – 2022
Principal Investigator – Operating Grant - $55,000 (CAD)
Predicting Clostridiodes difficile infection (CDI) recurrence employing a machine learning microbiome based artificial intelligence algorithm
Northern Ontario Academic Medicine Association, Health Sciences North and the Northern Medical School

2019 – 2022
Principal Investigator – Operating Grant - $25,000 (CAD)
Characterizing fatty liver disease in adolescents and young adults: A prospective feasibility study
TIME

2017 – 2020
Principal Investigator – Operating Grant - $1,200,000 (USD)
Microbes that matter: Defining optimal formulations for microbial ecosystem therapeutics
National Institute of Health (NIH)

Funding applied for

2020 – 2022
Co-Investigator – Weston Family Microbiome Initiative - $200,000 (CAD)
Allergic rhinitis microbiome study (ARMS): Analysis of Lactococcus lactis W136 on ragweed induced seasonal allergic rhinitis and the nasal microbiome
The W. Garfield Weston Foundation

2020 – 2022
Principle Investigator – Weston Family Microbiome Initiative - $200,000 (CAD)
Identification and characterization of novel therapeutic protease(s) for the treatment of clostridiodes difficile infection
The W. Garfield Weston Foundation

2020 – 2024
Co-Investigator – Project Grant - $1,000,000 (CAD)
Preventing HIV infection and pregnancy with the antimicrobial peptide LL-37: A novel multipurpose prevention technology
CIHR

Vanner

Current Funding

2020/06 – 2020/12
Principal Investigator – Rapid Response Queen's SARS-CoV-2/ COVID-19 Research Opportunity - $50,000 (CAD)
COVID-19 testing of health professional students: Informing testing and public policy for Universities and Society
Queen's University

2020
Principal Investigator – DOM Research Awards - $25,000 (CAD)
COVID-19 testing of health professional students: Informing testing and public policy for Universities and Society
Department of Medicine, Queen's University

2019 – 2022
Principal Investigator – Grant in Aid of Research - $375,000 (CAD)
Reducing IBD pain: targeting novel opioid G protein-coupled receptor signaling in DRG neurons
CCC

2019 – 2021
Co-Principal Investigator – IMAGINE Incubator Grant - $148,200 (CAD)
Biomarkers of diet-microbiota interactions in IBS
CIHR
Co-Principal Investigator: Bercik, Premysl

2017/12 – 2020/03
Principal Investigator – Accelerate Fellowship Program - $360,000 (CAD) ($180k came from CCC partner grant)
Mitacs

2017/04 – 2022/03
Principal Investigator – Project Grant - $688,500 (CAD)
Novel signaling mechanisms leading to pain in irritable bowel syndrome
CIHR

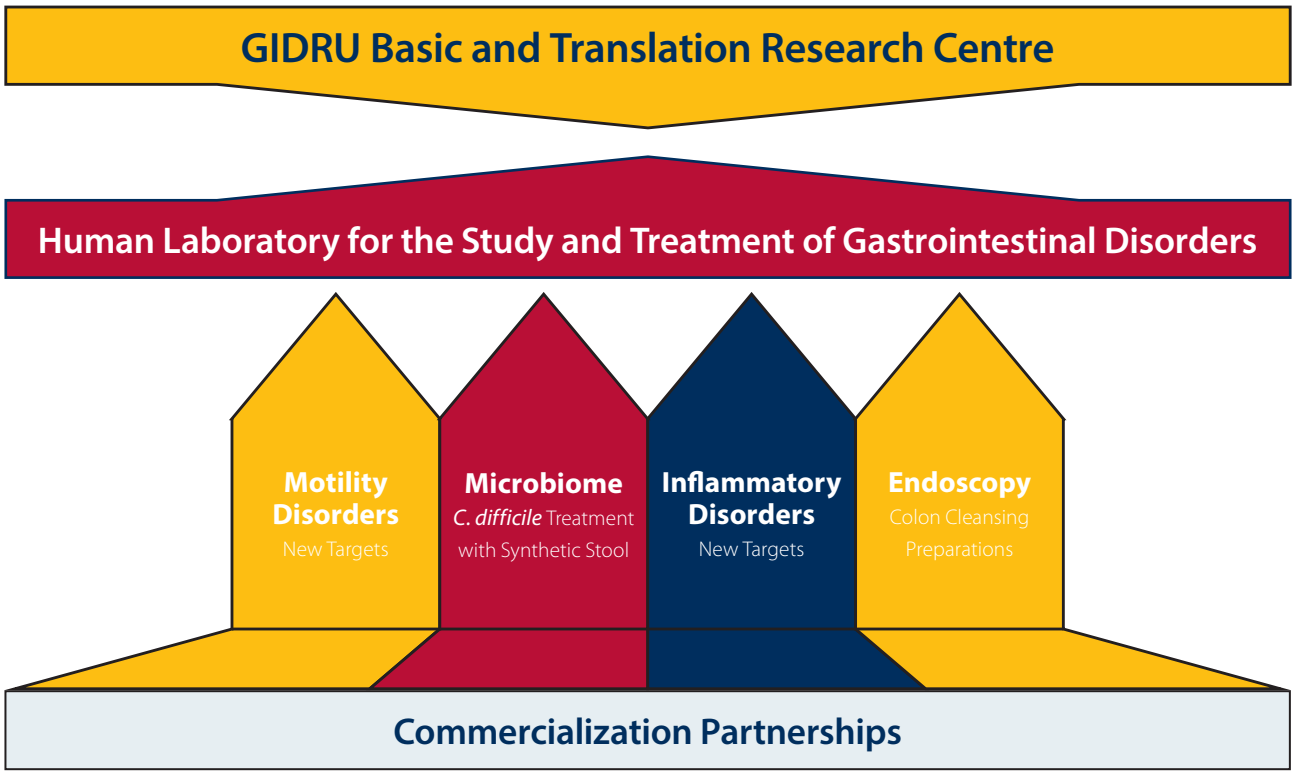
2015 - 2020
Co-Principal Investigator - SPOR Networks in Chronic Disease - $12,450,000 (CAD)
Inflammation, microbiome, and alimentation: gastro-intestinal and neuro-psychiatric effects: the IMAGINE-SPOR chronic disease network
CIHR

Funding applied for

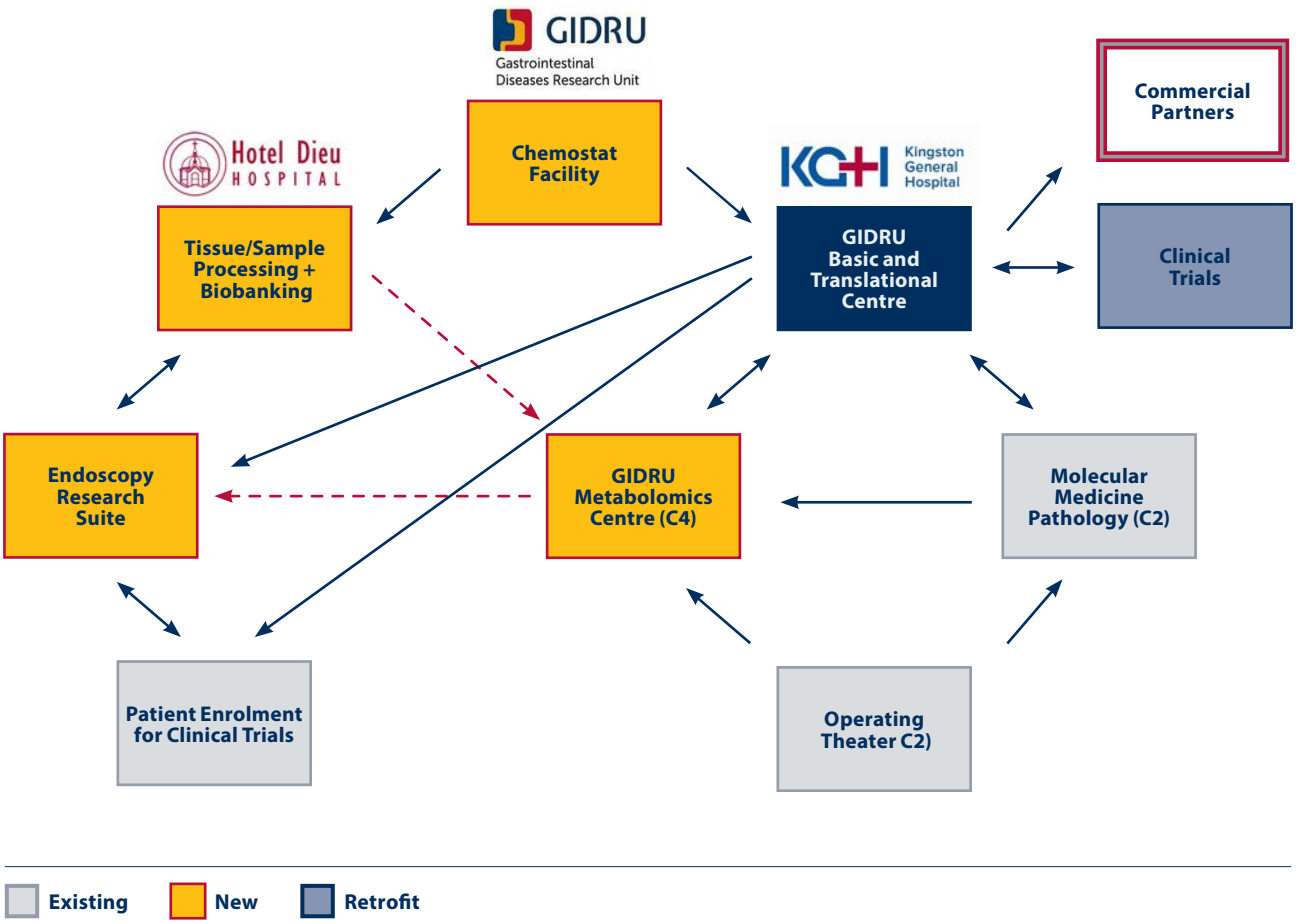
2020 – 2025
Nominated Principal Applicant – Project Grant - $1,405,000 (CAD)
Beyond the microbiota: Neuroactive metabolites underlying chronic abdominal pain
CIHR

Human Research Lab

SECTION III



Human Laboratory for the Study and Treatment of Gastrointestinal Disorders



New GIDRU Metabolomics Facility in the W.J. Henderson Centre (KHSC-KGH site).

Clinical Research

SECTION IV

ENDOSCOPIC RESEARCH

Dr. Hookey is the Medical Director of the KHSC endoscopy units at both sites, the past Regional Quality Lead for Endoscopy, and Canadian Association of Gastroenterology (CAG) Vice President, Clinical Affairs. He is now joined by Dr. Robert Bechara, who has completed advanced endoscopic training in Toronto and Tokyo, Japan.

Drs. Hookey and Bechara oversee the operations of the new research endoscopy suite. They are recognized internationally for their studies in colon cleansing for colonoscopy and their clinical trials involving new endoscopic techniques, including colon capsules, endoscopic retrograde cholangiopancreatography (ERCP) fistulotomy studies, and peroral endoscopic myotomy (POEM) achalasia research.

Conducting clinical studies within a busy clinical endoscopy suite is fraught with challenges: low patient recruitment, effective coordination of team members, time constraints preventing exploration of more basic science questions, lack of ready access to necessary expertise and to state-of-the-art facilities.

The endoscopic research facilities help overcome many of these challenges and is critical to the success of our human translational research program. This unique facility sets a new standard for research capacity, quality control and research capabilities, providing:

- On-demand access to endoscopic procedures resulting in the ability to complete studies rapidly. This facility will have the capacity to conduct a minimum of 10 procedures per day, five days per week. Therefore, 300 patients, for example, could potentially be enrolled within 6 weeks;
- Highest quality studies run by a team of established clinician-scientists, research nurses, and experienced study coordinators (all with Good Clinical Practice certification), dedicated to the facility, and unencumbered by clinical activities of a busy endoscopy suite;
- Mechanistic studies of gastrointestinal secretions, stool, tissue, blood, and urine samples facilitated by an affiliated state-of-the-art multidisciplinary basic science and clinical digestive health research centre (GIDRU);
- Full capacity to conduct investigator- and industry-driven clinical studies outside of standard clinical care, related to both endoscopic techniques and digestive diseases. Timely access to human ethics review and approval by institutional boards;
- Access to a large patient population through an attached outpatient facility with a full range of secondary and tertiary care for GI disorders, with experienced study coordinators embedded within the facility. There is also access to a large control group undergoing colon screening, but otherwise healthy;
- High-tech biobanking facility for secure storage of human biological specimens.

Melissa Kelley

Assistant Professor

CLINICAL TRIALS

Dr. Melissa Kelley has recently taken over as the Clinical Trials Director for the GI Division and has been supported by Dr. Hookey and Dr. Ropeleski in this new venture. She is also currently working on her MSc in Evidence Based Health Care through Oxford University and looks forward to starting her own research ventures in the near future.

The GI Division sees over 4000 patients annually in the outpatient clinic and conduct 3000 endoscopic procedures. Our research coordinators are imbedded in these activities; currently, they are overseeing 14 industry sponsored trials, 12 GIDRU investigator trials and 2 collaborative trials with PIs at other centres.

The CFI/OIT-funded "Human Laboratory for the Study and Treatment of Gastrointestinal Disorders" has greatly facilitated the potential for mechanistic clinical trials, in part through the development of a GIDRU-based biobank. Consequently, our translational research component continues to proceed at a brisk pace. A dedicated research assistant has played a pivotal role in our success thus far in acquiring tissue, blood and biospecimens. This has translated into the development of seamless mechanisms that are functioning both at the ambulatory clinic, the endoscopy centres at both hospitals, as well as in the operating room.

Collaborations continue to flourish at GIDRU. The establishment of a working team collaboration with members of the IBD clinical program and the Department of Psychology have been highly effective. We have successfully developed a team of researchers through our collaboration with Dr. Dean Tripp in the Department of Psychology into the clinical arena in the IBD clinic. This has involved integrating a research assistant into the busy clinic where patients have been actively enrolled into studies while receiving their clinical care at the same time. This required efficient use of space and the mobilization of awareness among physicians, nurses, medical student and student nurses as well as support personnel in the ambulatory clinic. We have a similar collaboration with leaders in the Department of Urology.

The ambulatory GI clinics continue to provide important opportunities for collaborations with members of the basic science departments. For example, ongoing studies are being carried out in IBD examining novel proteins of interest in patients with different states of intestinal inflammatory activity. Such preliminary data will serve as spring- boards for future research questions and studies examining functional immunological endpoints relevant to current views on the pathogenesis of IBD.

We maintain a blended program with respect to industry-sponsored clinical trials and investigator-driven clinical studies. We continue to focus efforts on providing patients, who have chronic diseases that are refractory to treatment, with an opportunity for enrollment into state-of-the-art clinical trials exploring new therapies. Studies are focused on disease prevention, treatment of ulcerative colitis as well as Crohn's disease, with a focus on providing patients with access to trials who are either biologic naïve or biologic experienced.

We also have established a framework for regular meetings of faculty and GI fellows to discuss aspects of the management of the translational research program, as well as providing updates on study approval/regulatory status, enrollment status, as well as infrastructure and personnel needs to facilitate us achieving our goals.

Melinda Allen July

Clinical Trials Coordinator

Aline Costa da Silva Asselstine

Research Assistant

Jodi Grifferty

Registered Dietician

Celine Morissette

Research Assistant

Chelsea Wilson

Lab Technician/Research Assistant

CLINICAL RESEARCH COORDINATORS

GIDRU has four highly skilled clinical trial and research coordinators and a registered dietician who work closely with GIDRU PI's to conduct clinical trials, perform patient sample collection and biobanking, and scheduling of mechanistic studies. Their performance has been critically acclaimed on numerous occasions by national and international clinical trial monitors. They have continuing education and certification in the conduct of clinical research including Good Clinical Practices, electronic data capture, and transportation of dangerous goods. They also have annual training in WHMIS and health and safety. They have enrolled thousands of patients and coordinated numerous local and collaborative studies in Canada (University of Toronto, McMaster, McGill), Europe, the US and Australia. They have also conducted numerous pharmaceutical clinical trials, working with both Health Canada and the FDA. Their roles provide a vital link between patients and the basic science capacity of GIDRU to facilitate the translation potential of the group.

GI FUNCTION LABORATORY

The GI Function Laboratory is a state-of-the-art clinical evaluation unit for non-invasive and invasive studies of gastrointestinal physiology and pathophysiology.

Patients can undergo upper (esophageal motility, 24h pH testing) and lower motility testing (anorectal motility, pudendal nerve studies), breath testing (lactose, lactulose, fructose, C13 Helicobacter pylori testing), stool analysis (weight, fecal fat, electrolytes), and biofeedback therapy under the supervision of fully trained biotechnologists and therapists. The facility enables both advanced standard-of-care studies and the ability to conduct high-quality, mechanistic clinical trials. It is ideally located adjacent to the outpatient clinic and endoscopy suites at the KHSC-HDH site, thus optimizing patient access.

Dr. Bechara

Achalasia is a disease of the esophagus that causes difficulty swallowing and can lead to significant disability. In this condition, the normal movements that help ingested food pass into the stomach are impaired. It is believed to be caused by a loss of nerve cells that control the contraction and relaxation of the muscle in the esophagus leading to a tightened lower esophagus. Little is known about how this occurs, and effective treatments historically were limited to invasive surgical procedures.

The POEM procedure is a new specialized treatment by specially trained gastroenterologists whereby an incision is made through a layer of muscle in the lower part of the esophagus using a gastroscope; this allows the lower esophagus remain open. This procedure has revolutionized the way achalasia is treated. We are thankful to have the capability to perform this procedure in Kingston.

POEM has also provided a new way of obtaining specimens of diseased esophageal muscle from patients that suffer from this disease. With this tissue, we can study the nerves and smooth muscles in patients with this disease in a way that has not yet been possible.

Since June 2017, we have been collecting patient data and specimens of muscular tissue during the POEM procedure. We have collected several samples from individuals that suffer from achalasia and have been studying how this disease affects the nerves and smooth muscle of the esophagus using advanced immunohistochemical testing. Our work is delineating the role of inflammatory cells in the evolution of this disease, and how this effects not only neurons but their axonal processes. We are also looking at how the muscular layer of the esophagus is changed which can impair its ability to function properly.

The insights that we gain from these experiments will further our knowledge of this disease and help develop considerations for other therapeutic options in the future.

Faculty Research

SECTION V

Dr. Blennerhassett

Crohn's disease causes severe transmural inflammation that causes thickening of the intestinal wall, which typically progresses to cause obstruction (stricturing) and the requirement for surgery. We focus on the molecular and cellular mechanisms of the growth of smooth muscle cells that contributes to this. Animal models have been invaluable for research, and we recently described a model of Crohn's disease that shows smooth muscle growth in both rats and mice.

Cultured rat and human intestinal smooth muscle cells showed that inflammation-induced proliferation caused epigenetic changes which blocked the expression of contractile proteins, with similar changes already present in Crohn's strictures. Our successful experimental reversal to restore phenotype suggests new approaches for human treatment.

A unique model of stricture formation showed that alternatively activated (M2) macrophages characterize the develop-

ing and established stricture, with smooth muscle growth and a progressive loss of phenotype. There was a loss of sensitivity to TGFβ, a factor from M2 macrophages that normally suppresses proliferation, and high levels of HIF-1α that permitted growth under the ischemic conditions in inflammation.

Overall, inflammation promotes stricture formation through key epigenetic alterations to smooth muscle that are susceptible to intervention and can form the basis for new therapeutics.

Papers:

- Blennerhassett et al. Analgesia and mouse strain influence neuromuscular plasticity in inflamed intestine. Neurogastroenterol Motil 29: 1-12, 2017.
- Bonafiglia et al. Epigenetic modification of intestinal smooth muscle cell phenotype during proliferation. Am J Physiol (Cell Physiol) 315: C722-C733, 2018.
- Lourenssen and Blennerhassett. M2 macrophages and phenotypic modulation of hyperplastic smooth muscle characterize Inflammatory stricture formation in the rat. Am J Path (in press, 06/2020).

Dr. Flemming

Dr. Flemming's research program focuses on health services research in cirrhosis and chronic liver disease with a particular focus on cirrhosis in young adults and women. The data used for the program is from ICES, which is an an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. Data from ICES is able to link routinely collected healthcare data from the over 14 million residents in Ontario. Using these linked datasets, she has validated a large cohort of over 200,000 patients with cirrhosis, which serves as the starting point for multiple epidemiologic studies related to cirrhosis and chronic liver disease.

Over the past year, Dr. Flemming, along with her team and trainees, have published data highlighting the increasing burden of cirrhosis in young adults and women (Flemming et al. Lancet Gastroenterology and Hepatology. 2019 Mar;4(3):217-226; Flemming JA et al. International Liver Congress 2020) and have contributed to the international discussion on cirrhosis epidemiology (Wang P and Flemming JA. Lancet Gastroenterology and Hepatology. 2020 Mar;5(3):230-231). Her research has highlighted that survival in patients with cirrhosis who received transjugular intrahepatic portotsystemic shunts is improved if they are performed in high volume versus low volume centres (Mah JM et al. Hepatol Comm. 2019 Mar 25;3(6):838-846). Importantly, work evaluating outcomes in pregnant women with cirrhosis has provided essential data for healthcare providers and patients regarding family planning discussions in women with cirrhosis (Flemming JA et al. Gastroenterology 2020, revision requested).

Over the next two years, funding from the Translational Institute of Medicine at Queen's University will allow Dr. Flemming and her GIDRU collaborators to develop a prospective cohort of adolescents and young adults with fatty liver disease, with collection of biospecimens to further characterize the natural history in this population.

Dr. Hookey

Dr. Hookey's research team continues to conduct clinical research investigating the best way to prepare for colonoscopy and capsule endoscopy. In 2019, ongoing research includes a prospective trial in conjunction with a team from Sheffield, England. This trial is a randomized controlled trial (RCT) of three different preparation regimens and could possibly settle the issue of which regimen to use definitively. Another ongoing study is an RCT to test the applicability of a phone application to enhance the use of bowel preparation regimens. We also published a paper in the Journal of the Canadian Association of Gastroenterology looking at how the results of these studies actually translate to real world experience (Does It work in Clinical Practice? A Comparison of Colonoscopy Cleansing Effectiveness in Clinical Practice Versus Efficacy from Selected Prospective Trials. Wang CN, Yang R, Hookey L.J Can Assoc Gastroenterol. 2020 Jun;3(3):111-119. doi: 10.1093/jcag/gwy070. Epub 2019 Feb 12. PMID: 32395685).

Dr. Lomax

Chronic abdominal pain is an intractable symptom of many gastrointestinal diseases, such as IBD. Our findings have revealed an important potential role for the gut microbiota in modulating this symptom (Sessenwein et al., 2017; Lomax et al., 2019; Pradhananga et al., 2020). The gut microbiota is a complex and dynamic microbial ecosystem that produces many compounds that affect human health. We have discovered that the gut microbiota of healthy individuals produces natural analgesic substances that exert tonic inhibitory effects on pain perception. IBD is associated with disturbances to the composition and metabolic output of the gut microbiota and our preliminary finds have identified that stool supernatants from these patients with abdominal pain have pronounced excitatory effects on pain perception that likely contribute to the pain these patients feel. Ongoing work aims to identify the molecules responsible for these pain-causing effects, characterize the microbial sources and delineate the host signaling pathways affected by these molecules. Ultimately, these insights may lead to development of novel therapeutics, including probiotics, that selectively block the painful effects of microbial dysbiosis.

Papers:

- Lomax AE, Pradhananga S, Sessenwein JL & O'Malley D. (2019). Bacterial modulation of visceral sensation: mediators and mechanisms. American journal of physiology Gastrointestinal and liver physiology 317, G363-G372.
- Pradhananga S, Tashtush AA, Allen-Vercoe E, Petrof EO & Lomax AE. (2020). Protease-dependent excitation of nodose ganglion neurons by commensal gut bacteria. The Journal of physiology 598, 2137-2151.
- Sessenwein JL, Baker CC, Pradhananga S, Maitland ME, Petrof EO, Allen-Vercoe E, Noordhof C, Reed DE, Vanner SJ & Lomax AE. (2017). Protease-Mediated Suppression of DRG Neuron Excitability by Commensal Bacteria. The Journal of neuroscience : the official journal of the Society for Neuroscience 37, 11758-11768.

Dr. Reed

Abdominal pain is the major cause of morbidity in patients with IBS. Food is a trigger of abdominal pain in a majority of IBS patients and our lab explores mechanisms by which food induces abdominal pain. Bile acids, released into the gut lumen after a meal, are increased in the colon in a subset of IBS patients. Recently, we demonstrated multiple mechanisms whereby bile acids can increase pain signaling in the colon (Yu et al, 2019). We are currently exploring other mechanisms whereby food can increase pain from the gut. For example, we have preliminary data that demonstrates when food antigens are present in the gut during the time of psychological stress, this sensitizes the gut such that re-ingestion of the food antigen increases pain signaling. Additionally, we have preliminary findings that an interaction of diet and the microbiota in a subset of IBS patients increases pain signaling. Our ongoing work aims to identify the pathways, both in the host tissue and the microbiota, in these scenarios that can result in meal-induced pain. Identification of these pathways may ultimately lead to specific therapeutic strategies for distinct subsets of IBS patients.

Papers:

- Yu Yang, Villalobos-Hernandez Egina C, Pradhananga Sabindra, Baker Corey C, Keating Christopher, Grundy David, Lomax Alan E, Reed David E. (2019). Deoxycholic acid activates colonic afferent nerves via 5-HT receptor-dependent and -independent mechanisms. American journal of physiology. Gastrointestinal and liver physiology, 317, G275-G284.

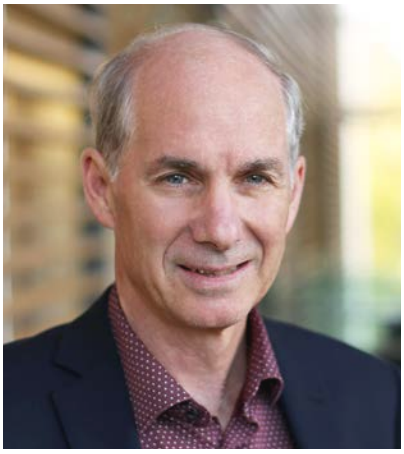
Dr. Sheth

The Sheth laboratory works on pathogen-host interactions and is a new addition to GIDRU. The main focus of our laboratory is to better understand how microorganisms (bacteria and viruses) interact with the host and how modifying the host environment can lead to improved health. We have the ability to

culture fastidious (difficult to grow) bacteria using specialized anaerobic chambers, as well as to evaluate the interplay of complex bacterial communities using continuous culture vessels. Our laboratory group works to develop microbial-based therapies for *C. difficile,* to study the development of bacterial resistance *in vitro*, and, more recently, to investigate the metabolomic profiles of patients infected with SARS-CoV-2, the causative agent of COVID-19.

Papers :

- Sheth P.M., Uyanwune Y., Laroque M., Douchant K., Anantharajah A., Borgundvaag E., Dales L., McCreight L., McGeer A., McNaught L., Moore C., Ragan K., Brouhanski G. Evidence of Transmission of *Clostridium difficile* in asymptomatic patients following admission screening in tertiary care hospital in Toronto. PLoS ONE 2019; 14(2) 1 - 14.
- Keshmiri R., Coyte P.C., Laporte A., Sheth P.M., Loutfy M. Cost-effectiveness analysis of infant feeding modalities for virally-suppressed mothers in Canada living with HIV. Medicine 2019; 98(23)e15841.



Dr. Vanner

The Vanner laboratory investigates the mechanisms causing intestinal pain in GI disorders, such as IBS and IBD. We do so through a combination of preclinical models and human studies. With our collaborators, we discovered novel intracellular signaling pathways in intestinal pain-sensing neurons (nociceptors) of IBS patients that trigger sustained pain signaling, often lasting for hours once activated. We determined that proteases originating from mast cells and/or gut microbiota activate these intracellular pathways. Using nanotechnology, we successfully blocked this signaling. Similar pathways were identified for opioid signaling during IBD, however, signaling through these pathways resulted in sustained inhibition of the nociceptors, or decreased pain signals. Therefore, blocking or activating these pathways, respectively, provides novel therapeutic targets.

We also examine diet-microbiota interactions in the gut as a potential source of mediators that elicit abdominal pain. We have found that complex carbohydrates increase histamine production by gut bacteria in subsets of IBS patients, and these mediators, in turn, sensitize nociceptors leading to enhanced pain signaling. Our findings support gut bacteriotherapy as a novel approach to treat pain in these patients.

Other exciting studies underway in our laboratory include investigating the use of pH-sensitive opioid drugs that only target inflamed colon (tissue pH is reduced in these tissues). Hence, these drugs could offer effective pain control in GI disorders, such as IBD, without the serious side effects often seen with opioid drugs. This is because other organs, such as the brain and lungs, are not inflamed and thus, not acted on by the drug. Our group is also investigating mechanisms of opioid tolerance in IBD. If we can prevent the induction of tolerance, than we have another means of mitigating unwanted opioid side effects by ensuring lower doses retain efficacy.

Papers:

- Jimenez-Vargas N.N., Gong J., Wisdom M., Jensen D.D., Latorre R., Hegron A., Teng S., DiCello J.J., Rajasekhar P., Veldhuis N.A., Carbone S.E., Yu Y., Lopez-Lopez C., Jaramillo-Polanco J., Canals M., Reed D.E., Lomax A.E., Schmidt B.L., Leong K., Vanner S.J., Halls M.L., Bunnett N.W., Poole D.P. 2020. Endosomal signaling of delta opioid receptors is an endogenous mechanism and therapeutic target for relief from inflammatory pain. Proc Natl Acad Sci USA. Accepted.
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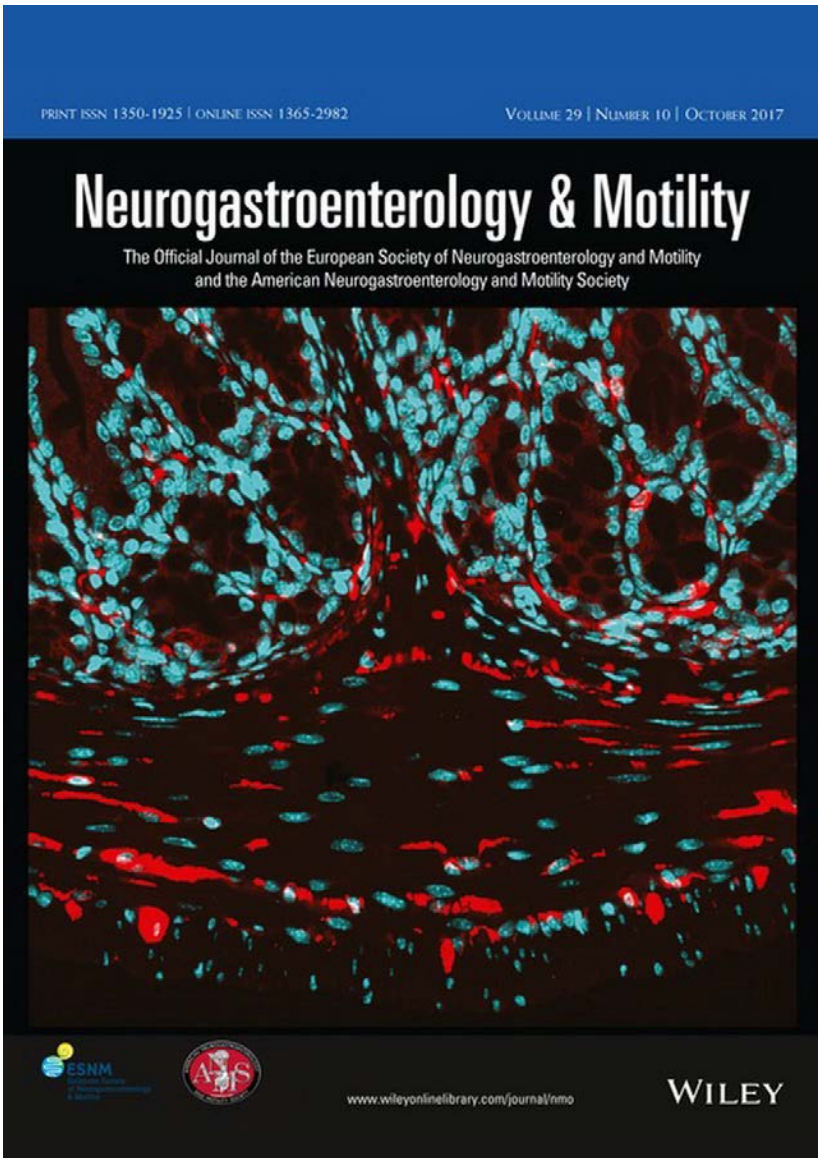
- McIntosh K., Reed D., Schneider, T., Dang F., Keshteli A. K., de Palma G., Madsen K., Bercik P., Vanner S. 2016. FODMAPs alter symptoms and the metabolome of irritable bowel syndrome patients: A randomized controlled trial. Gut 66(7):1241-1251.

Dr. Takami

Dr. Kaede Takami graduated with a PhD in Immunology and Microbiology from Dalhousie University and held a postdoctoral position at the Kidney Research Centre in Ottawa, before joining GIDRU in 2015. She serves as the manager of operations and also assists faculty and trainees with experimental design, and manuscript and grant development.

Publications

SECTION VI



Cover art for the Neurogastroenterology & Motility Journal is based on a figure in Dr. Blennerhassett's original article "Analgesia and mouse strain influence neuromuscular plasticity in inflamed intestine." [Blennerhassett MG, Lourenssen SR, Parlow LRG, Ghasemlou N, Winterborn AN (2017). Neurogastroenterology & Motility 29(10): 1-12]

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Trainees

SECTION VII

TRAINEES (2019 – 2020)

Bechara

Douglas Motomura, MD (Resident)

Amir Nazarin, MD (Resident)

Simon Hew, MD (Resident); *co-supervised by Dr. Hookey*

Roxy Chis, MD (Resident)

Bharat Markandey, MD (Resident)

Michael Scaffidi, MD (Resident)

Blennerhassett

Jay Kataria, MSc Candidate

Flemming

Doug Motomora, MD (Resident)

Monica Mullin, MD (Resident)

Jacquie Lu, MD (Resident)

Peter Wang, MD (Resident)

David Rodrigues, MD (Resident)

Mandip Rai, MD (Resident); *co-supervised by Dr. Hookey*

Susan Thanabalasingam, MD Candidate

Sasha Zarnke, MD Candidate

Zuhaib Mir, MSc Candidate

George Phillip, MSc Candidate

Hookey

Mandip Rai, MD (Resident); *co-supervised by Dr. Flemming*

Simon Hew, MD 2019 (Resident); *co-supervised by Dr. Bechara*

Lomax

Ayssar Tashtoush, PhD Candidate

Samira Osman, PhD Candidate

Amal Abu Omar, PhD Candidate; *co-supervised by Dr. Reed*

Reed. Bailey Brant, MSc Candidate; *co-supervised by Dr. Vanner*

Aidan Bennett, MSc Candidate

Corey Baker, MSc Candidate

Reed

Sean Bennet, PhD (PDF)*

Yang Yu, PhD (PDF)*

Cintya Lopez-Lopez, PhD (PDF)*

Amal Abu Omar, PhD Candidate; *co-supervised by Dr. Lomax*

Quentin Tsang, MSc Candidate*

** co-supervised by Dr. Vanner*

Sheth

Mabel Guzman-Rodriguez, PhD (PDF)

Katya Douchant, PhD Candidate

Emily Moslinger, MSc Candidate

Kevin Richards, MSc Candidate

Vanner

Nestor Jiminez Vargas, PhD (PDF)

Josué Jaramillo-Polanco, PhD (PDF)*

Cintya López-López, PhD (PDF)*

Yang Yu, PhD (PDF)*

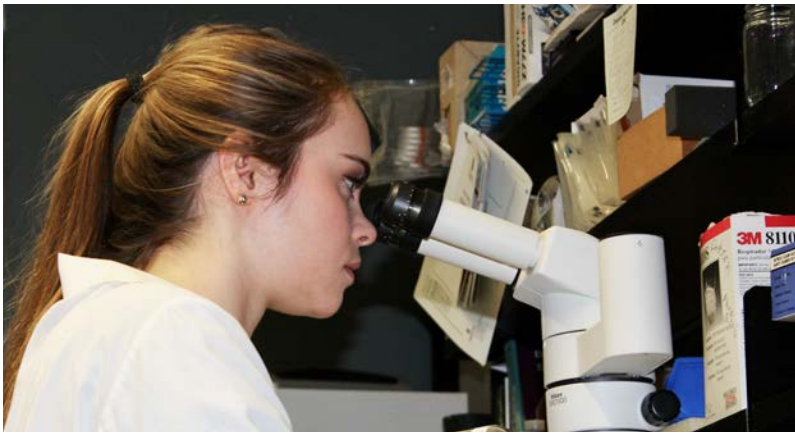
Sean Bennett, PhD (PDF)*

Claudius Degro, MD (PDF; starting October 2020)

Quentin Tsang, MSc Candidate*

Bailey Brant, MSc Candidate; *co-supervised by Dr. Lomax*

** co-supervised by Dr. Reed*



New Programs

SECTION VIII

Microbiota Ecosystem Therapeutics

Dr. Elaine Petrof's group, in collaboration with Dr. Allen-Vercoe at the University of Guelph, created the first synthetic stool "33 strain" probiotic. With their GIDRU collaborators, they proceeded to conduct the "first-in-the-world" studies showing that it effectively cures *C. difficile* colitis in patients who are unresponsive to antibiotics. This remarkable advance (Microbiome 2013, cited 392 times) was made possible by the chemostat culture of previously "unculturable" bacteria that represent much of the human microbiota. The discovery was instrumental in our receiving the CFI/OIT award to build our state-of-the-art chemostat facility. With Dr. Petrof's retirement, this facility is now led by newly recruited Dr. Prameet Sheth. His expertise and this world-class research infrastructure are paving the way for the development of ecosystem therapeutics trials to treat many health disorders.

GIDRU-CAUR Partnership

As part of a collaboration with the Centre for Applied Urological Research (CAUR), GIDRU researchers are examining the link between psychological stress and gastrointestinal disorders. Using their combined expertise, Dr. Dean Tripp, psychologist at CAUR and Dr. Mike Beyak, GIDRU clinician-scientist, have received funding from Crohn's and Colitis Canada to examine psychological factors and pain in IBD. These collaborations have spawned new research initiatives, including COVID-19 research into the psychological impact of the pandemic on the health and well-being of Queen's students.

ICES Database Studies

GIDRU will further expand its translational program through the contributions of Dr. Jennifer Flemming, a clinician-scientist from the Institute for Clinical Evaluative Sciences (ICES). She will harness the wealth of information found in ICES databases to investigate liver disease and related malignancies.

Human Sample Profiling

GIDRU will continue to broaden its translational program by capitalizing on its CFI/OIT-funded and fully operational Human Digestive Disease Laboratory. The biobanking component of this Laboratory, located at the Hotel Dieu Hospital site of the Kingston Health Sciences Centre, has led to multiple, ongoing collaborations with members of both Queen's Departments of Biomedical & Molecular Sciences and Pathology & Molecular Medicine. These projects include the molecular profiling of blood and tissue samples using cutting-edge platforms, such as next-generation sequencing and nanotechnology. Moreover, GIDRU is a superuser at the Queen's CardioPulmonary Unit (QCPU), providing its members access to the state-of-the-art molecular and imaging facilities available at QCPU.

External Collaborative Research Programs

GIDRU members have established strong, fruitful collaborations with McMaster's researchers at the Farncombe Institute that involve the study of diet-microbiota interactions underlying pain signaling in the GI tract. This collaboration, taking advantage of complementary skills and infrastructure at both sites (microbiome and germ-free mouse facility at McMaster; electrophysiology expertise at Queen's), has already led to 4 joint publications, as well as grant application submissions to the Weston Foundation and the Canadian Institutes of Health Research (CIHR). GIDRU also has longstanding collaborations with researchers, such as Dr. Nigel Bunnett at NYU in New York City (over 15 joint publications), which again harnesses complementary expertise and promises to lead to many more exciting discoveries.

GIDRU Gastrointestinal Diseases Research Unit

Contact us

Faculty members can be contacted directly using the details on their laboratory pages:
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